I hereby certify that this correspondence is being electronically filed in the United States Patent and Trademark Office on June 19, 2009.

Frank C Eisenschenk

Frank C. Eisenschenk, Ph.D., Patent Attorney

REQUEST FOR CERTIFICATE OF CORRECTION UNDER 37 CFR 1.322
Docket No. C.R.102
Patent No. 7,531,508

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Richard Joseph Fagan, Christopher Benjamin Phelps, Tania Maria Rodrigues, Melanie Yorke, Mariastella De Tiani
Issued	:	May 12, 2009
Patent No.	:	7,531,508
Conf. No.	:	1704
For	:	Splice Variant of the Human Pituitary Growth Hormone

Mail Stop Certificate of Corrections Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR CERTIFICATE OF CORRECTION
UNDER 37 CFR 1.322 (OFFICE MISTAKE)

Sir:

A Certificate of Correction for the above-identified patent has been prepared and is attached hereto.

In the left-hand column below is the column and line number where errors occurred in the patent. In the right-hand column is the page and line number in the application where the correct information appears.

Patent Reads:	**Application Reads:**
Column 2, line 48:	Page 3, line 9:
"August;29 (8):16424)"	--Aug;29(8):1642-4--

Patent Reads:	**Application Reads:**
Column 16, line 49:	Page 23, line 24:
"fill-length"	--full-length--
Column 16, line 55:	Page 23, line 29:
"purposes of illusion"	--purposes of illustration--
Column 17, line 31:	Page 24, line 26:
"fill length"	--full length--
Column 21, line 4:	Page 30, line 1:
"5,693,506 5,659,122; and"	--5,693,506; US 5,659,122; and--
Columns 39-40, Table 1:	Page 56, Table 1:
"INSP101-3'-F AGG AGT TTG TAA GCT CTT GGG GAA TGG AGT CTA TTC CGA TGT CAA AGG CC (SEQ ID NO: 15)"	--INSP101-3'-F AGG AGT TTG TAA GCT CTT GGG GAA TGG AGT CTA TTC CGA CAC CCT CCA ACA (SEQ ID NO: 15)--
Column 42, SEQ ID NO: 3:	Page 61, SEQ ID NO: 3:
"1 AGTCTATTCC GAGACCCTCC AACAGGGAGG AAACACAACA GAAATCC"	--1 AGTCTATTCC GACACCCTCC AACAGGGAGG AAACACAACA GAAATCC--
Column 43, SEQ ID NO: 6:	Page 61, SEQ ID NO: 6:
"1 GSRTSLLLAF GLLCLPWLQE GSAFPTIPLS RLFDNAMLRA KRLHQLAFDT 51 YQEFVSSWGM ESIPTPSNRE ETQQKS"	--1 GSRTSLLLAF GLLCLPWLQE GSAFPTIPLS RLFDNAMLRA HRLHQLAFDT 51 YQEFVSSWGM ESIPTPSNRE ETQQKS--
Column 43, SEQ ID NO: 9:	Page 62, line 28, SEQ ID NO: 9:
"51 CCATCGTCTG CACCAGCTGG CCTTTGACAC CTACCACGAG TTTGTAAGGT"	--51 CCATCGTCTG CACCAGCTGG CCTTTGACAC CTACCAGGAG TTTGTAAGCT--.

A true and correct copy of pages 3, 23, 24, 30, 61 and 62 of the specification as filed which support Applicants' assertion of the errors on the part of the Patent Office accompanies this Certificate of Correction.

Approval of the Certificate of Correction is respectfully requested.

Respectfully submitted,

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FCE/jlr/sl

Attachments: Copy of pages 3, 23, 24, 30, 61 and 62

S.P., Sawyers C.L., and Pollak M. (2001) Cancer Res. Aug 15;61(16):6276-80), cardiovascular disease (Liu Y., Ding J., Bush T.L., Longenecker J.C., Nieto F.J., Golden S.H., and Szklo M. (2001) Am. J. Epidemiol. Sep 15;154(6):489-94), metabolic diseases (Flyvbjerg A. (2001) Growth Horm. IGF Res. Jun;11 Suppl. A:S115-9, Diamond T., Levy S., Smith A., Day P. and Manoharan A. (2001) Intern. Med. J. Jul;31(5):272-8, Toprak S., Yonem A., Cakir B., Guler S., Azal O., Ozata M., and Corakci A. (2001) Horm. Res.;55(2):65-70), inflammation (McEvoy A.N., Bresnihan B., FitzGerald O., and Murphy E.P. (2001) Arthritis Rheum. Aug;44(8):1761-7, Lipsett P.A. (2001) Crit. Care Med. Aug;29(8):1642-4) and CNS related diseases (Bowen R.L. (2001) JAMA. Aug 15;286(7):790-1).

Growth Hormone family

Growth hormone is a member of a family of polypeptide hormones that share structural similarities and biological activities and are produced in the pituitary glands of all vertebrates and the placentae of some mammals. Family members include pituitary prolactin, placental lactogens (also called chorionic somatomammotropins in humans [hCS]), prolactin-related proteins in ruminants and rodents, proliferins in mice, and somatolactin in fish.

The genes that encode most members of the GH family comprise five exons and four introns and appear to have arisen by duplication of a single ancestral gene prior to the appearance of the vertebrates. Splicing and processing variants have been described for several members of the family.

The human GH-related gene family located on chromosome 17q22-24 consists of a gene cluster of highly sequence-conserved genes and a single prolactin gene on chromosome 6 (Owerbach D. *et al.* Science 1981). The gene cluster includes five structural genes, two GH and three CS genes, whose expression is tissue specific: hGH-N (N=normal), hGH-V (V=variant), human chorionic somatomammotropin hormone-like (hCS-L), human chorionic somatomammotropin A and B (hCS-A and hCS-B) (Misra-Press, A *et al.* JBC 1994; Boguszewski C. *et al.* JBC 1998).

The GH -related family of proteins has shared structural similarities since their tertiary structure form four ∝-helices, also known as a four antiparallel helix bundle. The ∝-helices are tightly packed and arranged in an antiparallel up-up-down-down orientation, with two long loops linking the parallel pairs.

comprising 50% formamide, 5XSSC (150mM NaCl, 15mM trisodium citrate), 50mM sodium phosphate (pH7.6), 5x Denhardts solution, 10% dextran sulphate, and 20 microgram/ml denatured, sheared salmon sperm DNA, followed by washing the filters in 0.1X SSC at approximately 65°C. Low stringency conditions involve the hybridisation reaction being carried out at 35°C (see Sambrook *et al.* [*supra*]). Preferably, the conditions used for hybridization are those of high stringency.

Preferred embodiments of this aspect of the invention are nucleic acid molecules that are at least 90% identical over their entire length to a nucleic acid molecule encoding the INSP101 nucleic acid molecules that are substantially complementary to such nucleic acid molecules.

Preferably, a nucleic acid molecule according to this aspect of the invention comprises a region that is at least 92% identical over its entire length to such coding sequences, or is a nucleic acid molecule that is complementary thereto. In this regard, nucleic acid molecules at least 95%, preferably at least 98% or 99% identical over their entire length to the same are particularly preferred. Preferred embodiments in this respect are nucleic acid molecules that encode polypeptides which retain substantially the same biological function or activity as the INSP101 polypeptides.

The invention also provides a process for detecting a nucleic acid molecule of the invention, comprising the steps of: (a) contacting a nucleic probe according to the invention with a biological sample under hybridizing conditions to form duplexes; and (b) detecting any such duplexes that are formed.

As discussed additionally below in connection with assays that may be utilised according to the invention, a nucleic acid molecule as described above may be used as a hybridization probe for RNA, cDNA or genomic DNA, in order to isolate full-length cDNAs and genomic clones encoding the INSP101 polypeptides and to isolate cDNA and genomic clones of homologous or orthologous genes that have a high sequence similarity to the gene encoding this polypeptide.

In this regard, the following techniques, among others known in the art, may be utilised and are discussed below for purposes of illustration. Methods for DNA sequencing and analysis are well known and are generally available in the art and may, indeed, be used to practice many of the embodiments of the invention discussed herein. Such methods may employ such enzymes as the Klenow fragment of DNA polymerase I, Sequenase (US

Biochemical Corp, Cleveland, OH), Taq polymerase (Perkin Elmer), thermostable T7 polymerase (Amersham, Chicago, IL), or combinations of polymerases and proof-reading exonucleases such as those found in the ELONGASE Amplification System marketed by Gibco/BRL (Gaithersburg, MD). Preferably, the sequencing process may be automated using machines such as the Hamilton Micro Lab 2200 (Hamilton, Reno, NV), the Peltier Thermal Cycler (PTC200; MJ Research, Watertown, MA) and the ABI Catalyst and 373 and 377 DNA Sequencers (Perkin Elmer).

One method for isolating a nucleic acid molecule encoding a polypeptide with an equivalent function to that of the INSP101 polypeptides is to probe a genomic or cDNA library with a natural or artificially-designed probe using standard procedures that are recognised in the art (see, for example, "Current Protocols in Molecular Biology", Ausubel *et al.* (eds). Greene Publishing Association and John Wiley Interscience, New York, 1989,1992). Probes comprising at least 15, preferably at least 30, and more preferably at least 50, contiguous bases that correspond to, or are complementary to, nucleic acid sequences from the appropriate encoding gene (SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7 or SEQ ID NO:9) are particularly useful probes. Such probes may be labelled with an analytically-detectable reagent to facilitate their identification. Useful reagents include, but are not limited to, radioisotopes, fluorescent dyes and enzymes that are capable of catalysing the formation of a detectable product. Using these probes, the ordinarily skilled artisan will be capable of isolating complementary copies of genomic DNA, cDNA or RNA polynucleotides encoding proteins of interest from human, mammalian or other animal sources and screening such sources for related sequences, for example, for additional members of the family, type and/or subtype.

In many cases, isolated cDNA sequences will be incomplete, in that the region encoding the polypeptide will be cut short, normally at the 5' end. Several methods are available to obtain full length cDNAs, or to extend short cDNAs. Such sequences may be extended utilising a partial nucleotide sequence and employing various methods known in the art to detect upstream sequences such as promoters and regulatory elements. For example, one method which may be employed is based on the method of Rapid Amplification of cDNA Ends (RACE; see, for example, Frohman *et al.*, PNAS USA 85, 8998-9002, 1988). Recent modifications of this technique, exemplified by the Marathon™ technology (Clontech Laboratories Inc.), for example, have significantly simplified the search for longer cDNAs. A slightly different technique, termed "restriction-site" PCR, uses universal primers to

in US 5,693,506; US 5,659,122; and US 5,608,143. Additional examples of genetic expression in plant cell culture has been described by Zenk, Phytochemistry 30, 3861-3863 (1991).

In particular, all plants from which protoplasts can be isolated and cultured to give whole regenerated plants can be utilised, so that whole plants are recovered which contain the transferred gene. Practically all plants can be regenerated from cultured cells or tissues, including but not limited to all major species of sugar cane, sugar beet, cotton, fruit and other trees, legumes and vegetables.

Examples of particularly preferred bacterial host cells include *streptococci, staphylococci, E. coli, Streptomyces* and *Bacillus subtilis* cells.

Examples of particularly suitable host cells for fungal expression include yeast cells (for example, *S. cerevisiae*) and *Aspergillus* cells.

Any number of selection systems are known in the art that may be used to recover transformed cell lines. Examples include the herpes simplex virus thymidine kinase (Wigler, M. *et al.* (1977) Cell 11:223-32) and adenine phosphoribosyltransferase (Lowy, I. *et al.* (1980) Cell 22:817-23) genes that can be employed in tk^- or $aprt^\pm$ cells, respectively.

Also, antimetabolite, antibiotic or herbicide resistance can be used as the basis for selection; for example, dihydrofolate reductase (DHFR) that confers resistance to methotrexate (Wigler, M. *et al.* (1980) Proc. Natl. Acad. Sci. 77:3567-70); npt, which confers resistance to the aminoglycosides neomycin and G-418 (Colbere-Garapin, F. *et al* (1981) J. Mol. Biol. 150:1-14) and als or pat, which confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively. Additional selectable genes have been described, examples of which will be clear to those of skill in the art.

Although the presence or absence of marker gene expression suggests that the gene of interest is also present, its presence and expression may need to be confirmed. For example, if the relevant sequence is inserted within a marker gene sequence, transformed cells containing the appropriate sequences can be identified by the absence of marker gene function. Alternatively, a marker gene can be placed in tandem with a sequence encoding a polypeptide of the invention under the control of a single promoter. Expression of the marker gene in response to induction or selection usually indicates expression of the tandem gene as well.

List of INSP101 specific sequences (Note: for amino acids encoded by exon-exon junctions, the amino acid will be assigned to the more 5' exon.)

SEQ ID NO: 1 (INSP101 nucleotide sequence exon 2nov)

```
  1 GGCTCCCGGA CGTCCCTGCT CCTGGCTTTT GGCCTGCTCT GCCTGCCCTG
 51 GCTTCAAGAG GGCAGTGCCT TCCCAACCAT TCCCTTATCC AGGCTTTTTG
101 ACAACGCTAT GCTCCGCGCC CATCGTCTGC ACCAGCTGGC CTTTGACACC
151 TACCAGGAGT TTGTAAGCTC TTGGGGAATG G
```

SEQ ID NO: 2 (INSP101 protein sequence exon 2nov)

```
  1 GSRTSLLLAF GLLCLPWLQE GSAFPTIPLS RLFDNAMLRA HRLHQLAFDT
 51 YQEFVSSWGM E
```

SEQ ID NO: 3 (INSP101 nucleotide sequence exon 3nov)

```
  1 AGTCTATTCC GACACCCTCC AACAGGGAGG AAACACAACA GAAATCC
```

SEQ ID NO: 4 (INSP101 protein sequence exon 3nov)

```
  1 SIPTPSNREE TQQKS
```

SEQ ID NO: 5 (INSP101 contiguous nucleotide sequence exons 2nov and 3nov)

```
  1 GGCTCCCGGA CGTCCCTGCT CCTGGCTTTT GGCCTGCTCT GCCTGCCCTG
 51 GCTTCAAGAG GGCAGTGCCT TCCCAACCAT TCCCTTATCC AGGCTTTTTG
101 ACAACGCTAT GCTCCGCGCC CATCGTCTGC ACCAGCTGGC CTTTGACACC
151 TACCAGGAGT TTGTAAGCTC TTGGGGAATG GAGTCTATTC CGACACCCTC
201 CAACAGGGAG GAAACACAAC AGAAATCC
```

SEQ ID NO: 6 (INSP101 contiguous protein sequence exons 2nov and 3nov)

```
  1 GSRTSLLLAF GLLCLPWLQE GSAFPTIPLS RLFDNAMLRA HRLHQLAFDT
 51 YQEFVSSWGM ESIPTPSNRE ETQQKS
```

SEQ ID NO: 7 (INSP101 full length nucleotide sequence)

```
   1 ATGGCTACAG GCTCCCGGAC GTCCCTGCTC CTGGCTTTTG GCCTGCTCTG
  51 CCTGCCCTGG CTTCAAGAGG GCAGTGCCTT CCCAACCATT CCCTTATCCA
 101 GGCTTTTTGA CAACGCTATG CTCCGCGCCC ATCGTCTGCA CCAGCTGGCC
 151 TTTGACACCT ACCAGGAGTT TGTAAGCTCT TGGGGAATGG AGTCTATTCC
 201 GACACCCTCC AACAGGGAGG AAACACAACA GAAATCCAAC CTAGAGCTGC
 251 TCCGCATCTC CCTGCTGCTC ATCCAGTCGT GGCTGGAGCC CGTGCAGTTC
 301 CTCAGGAGTG TCTTCGCCAA CAGCCTGGTG TACGGCGCCT CTGACAGCAA
 351 CGTCTATGAC CTCCTAAAGG ACCTAGAGGA AGGCATCCAA ACGCTGATGG
 401 GGAGGCTGGA AGATGGCAGC CCCCGGACTG GGCAGATCTT CAAGCAGACC
 451 TACAGCAAGT TCGACACAAA CTCACACAAC GATGACGCAC TACTCAAGAA
 501 CTACGGGCTG CTCTACTGCT TCAGGAAGGA CATGGACAAG GTCGAGACAT
 551 TCCTGCGCAT CGTGCAGTGC CGCTCTGTGG AGGGCAGCTG TGGCTTCTAG
```

SEQ ID NO: 8 (INSP101 full length protein sequence)

```
   1 MATGSRTSLL LAFGLLCLPW LQEGSAFPTI PLSRLFDNAM LRAHRLHQLA
  51 FDTYQEFVSS WGMESIPTPS NREETQQKSN LELLRISLLL IQSWLEPVQF
 101 LRSVFANSLV YGASDSNVYD LLKDLEEGIQ TLMGRLEDGS PRTGQIFKQT
 151 YSKFDTNSHN DDALLKNYGL LYCFRKDMDK VETFLRIVQC RSVEGSCGF
```

SEQ ID NO: 9 (INSP101 full length nucleotide sequence– without signal peptide region)

```
   1 TTCCCAACCA TTCCCTTATC CAGGCTTTTT GACAACGCTA TGCTCCGCGC
  51 CCATCGTCTG CACCAGCTGG CCTTTGACAC CTACCAGGAG TTTGTAAGCT
 101 CTTGGGGAAT GGAGTCTATT CCGACACCCT CCAACAGGGA GGAAACACAA
 151 CAGAAATCCA ACCTAGAGCT GCTCCGCATC TCCCTGCTGC TCATCCAGTC
 201 GTGGCTGGAG CCCGTGCAGT TCCTCAGGAG TGTCTTCGCC AACAGCCTGG
 251 TGTACGGCGC CTCTGACAGC AACGTCTATG ACCTCCTAAA GGACCTAGAG
 301 GAAGGCATCC AAACGCTGAT GGGGAGGCTG GAAGATGGCA GCCCCCGGAC
 351 TGGGCAGATC TTCAAGCAGA CCTACAGCAA GTTCGACACA AACTCACACA
 401 ACGATGACGC ACTACTCAAG AACTACGGGC TGCTCTACTG CTTCAGGAAG
 451 GACATGGACA AGGTCGAGAC ATTCCTGCGC ATCGTGCAGT GCCGCTCTGT
 501 GGAGGGCAGC TGTGGCTTCT AG
```

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,531,508

APPLICATION NO.: 10/537,142

DATED : May 12, 2009

INVENTORS : Richard Joseph Fagan, Christopher Benjamin Phelps, Tania Maria Rodrigues, Melanie Yorke, Mariastella De Tiani

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 2,
Line 48, "August;29 (8):16424)" should read --Aug;29(8):1642-4--.

Column 16,
Line 49, "fill-length" should read --full-length--.
Line 55, "purposes of illusion" should read --purposes of illustration--.

Column 17,
Line 31, "fill length" should read --full length--.

Column 21,
Line 4, "5,693,506 5,659,122; and" should read --5,693,506; 5,659,122; and--.

Columns 39-40,
Table 1, "INSP101-3'-F AGG AGT TTG TAA GCT CTT GGG GAA TGG AGT CTA TTC CGA TGT CAA AGG CC (SEQ ID NO: 15)" should read --INSP101-3'-F AGG AGT TTG TAA GCT CTT GGG GAA TGG AGT CTA TTC CGA CAC CCT CCA ACA (SEQ ID NO: 15)--.

Column 42,
SEQ ID NO: 3, "1 AGTCTATTCC GAGACCCTCC AACAGGGAGG AAACACAACA GAAATCC" should read --1 AGTCTATTCC GACACCCTCC AACAGGGAGG AAACACAACA GAAATCC--.

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

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Column 43,

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51 YQEFVSSWGM ESIPTPSNRE ETQQKS"

should read --1 GSRTSLLLAF GLLCLPWLQE GSAFPTIPLS RLFDNAMLRA HRLHQLAFDT
51 YQEFVSSWGM ESIPTPSNRE ETQQKS--.

SEQ ID NO: 9, "51 CCATCGTCTG CACCAGCTGG CCTTTGACAC CTACCACGAG TTTGTAAGGT"

should read --51 CCATCGTCTG CACCAGCTGG CCTTTGACAC CTACCAGGAG TTTGTAAGCT--.

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